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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/297,486	06/14/1999	JOHN FRANCIS MARTIN	GJE-30	9834

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	23

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/297,486	Martin et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 5, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-9* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 22 on 3/5/03.

Claims 14, 15, and 37 were canceled by amendment in Paper No. 19, filed 1/25/02.

Claims 1-9 remain pending and are under consideration in this Office Action.

Applicant received a rejection on 8/19/02 (Paper No. 1 8) which was ambiguous with regard to its finality. The PTO form 326 stated that the action was non-final whereas the text of the action declared finality. In a subsequent communication from the Office, Applicant was led to believe that the rejection in Paper No. 18 was non-final. In view of the resulting confusion, and the following new grounds of rejection, finality of Paper No. 18 is withdrawn.

Specification

The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-Reference to Related Applications.

(c) Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).

(e) Background of the Invention.

1. Field of the Invention.

2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(i) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

Content of Specification

(a) Title of the Invention: See 37 CFR 1.72(a) and MPEP § 606. The title of the invention should be placed at the top of the first page of the specification. It should be brief but

technically accurate and descriptive, preferably from two to seven words may not contain more than 500 characters.

(b) Cross-References to Related Applications: See 37 CFR 1.78 and MPEP § 201.11.

(c) Statement Regarding Federally Sponsored Research and Development: See MPEP § 310.

(d) Reference to a "Microfiche Appendix": See 37 CFR 1.96(c) and MPEP § 608.05, if the application was filed before March 1, 2001. The total number of microfiche and the total number of frames should be specified. Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc and an incorporation by reference of the material on the compact disc.

(e) Background of the Invention: See MPEP § 608.01(c). The specification should set forth the Background of the Invention in two parts:

(1) Field of the Invention: A statement of the field of art to which the invention pertains. This statement may include a paraphrasing of the applicable U.S. patent classification definitions of the subject matter of the claimed invention. This item may also be titled "Technical Field."

(2) Description of the Related Art: A description of the related art known to the applicant and including, if applicable, references to specific related art and problems involved in the prior art which are solved by the applicant's invention. This item may also be titled "Background Art."

(f) Brief Summary of the Invention: See MPEP § 608.01(d). A brief summary or general statement of the invention as set forth in 37 CFR 1.73. The summary is separate and distinct from the abstract and is directed toward the invention rather than the disclosure as a whole. The summary may point out the advantages of the invention or how it solves problems previously existent in the prior art (and preferably indicated in the Background of the Invention). In chemical cases it should point out in general terms the utility of the invention. If possible, the nature and gist of the invention or the inventive concept should be set forth. Objects of the invention should be treated briefly and only to the extent that they contribute to an understanding of the invention.

(g) Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f). A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

(h) Detailed Description of the Invention: See MPEP § 608.01(g). A description of the preferred embodiment(s) of the invention as required in 37 CFR 1.71. The description

should be as short and specific as is necessary to describe the invention adequately and accurately. Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail. However, where particularly complicated subject matter is involved or where the elements, compounds, or processes may not be commonly or widely known in the field, the specification should refer to another patent or readily available publication which adequately describes the subject matter.

(i) Claim or Claims: See 37 CFR 1.75 and MPEP § 608.01(m). The claim or claims must commence on separate sheet (37 CFR 1.52(b)). Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation. There may be plural indentations to further segregate subcombinations or related steps. See 37 CFR 1.75 and MPEP § 608.01(i)-(p).

(j) Abstract of the Disclosure: A brief narrative of the disclosure as a whole in a single paragraph of 150 words or less commencing on a separate sheet following the claims.

(k) Drawings: See 37 CFR 1.81, 1.83-1.85, and MPEP § 608.02.

(l) Sequence Listing, if on paper: See 37 CFR 1.821-1.825.

Claim Objections

Claim 1 is objected to because it contains the acronym VEGF. Applicant should amend the first claim containing a given acronym to contain the full name of what is implied by the acronym. For example, claim 1 should be amended to contain the full name "vascular endothelial growth factor", and to include the acronyms VEGF parenthetically after the full name.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting intimal hyperplasia at a site in a blood vessel in a rabbit by periadventitial administration at the site of a DNA expression vector encoding vascular endothelial growth factor (VEGF), does not reasonably provide enablement for treatment of any vascular disorder in any species other than a rabbit, and does not reasonably provide enablement for treatment of any vascular disorder in any species using any VEGF receptor agonist other than VEGF. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in Paper Nos. 15 and 18.

The claimed invention embraces methods of treatment or prevention of intimal hyperplasia (claims 1-9). The recited method steps require administration of a nucleic acid encoding an agonist a Flt-1 or Flk-1/KDR receptor to which VEGF binds. The nucleic acid must be delivered periadventitially to a site of injury, but there is no nexus between any site of injury and any hyperplastic site. As such the claims do not require treatment of hyperplasia at the site of nucleic acid delivery. In other words, the claims broadly read upon treatment of intimal hyperplasia by administration of nucleic acids at periadventitial sites distal to the site of the disease. The claims also embrace a range of effects from inhibition to complete prevention of intimal hyperplasia, as well as reversal of existing hyperplasia.

The specification teaches a working example in which plasmid expression vectors encoding VEGF were complexed with liposomes and delivered to the adventitial surface of a rabbit carotid artery underneath a silicone collar. It was previously shown that placement of a silicone collar on a rabbit carotid artery causes intimal hyperplasia. Injection of VEGF plasmid/liposome complexes inhibited intimal hyperplasia, but that this inhibition decreased after two weeks, probably due to a loss of transient gene expression. See the specification at page 33, lines 11-22, and page 36, lines 20-26. The specification does not exemplify complete prevention of intimal hyperplasia, or reversal of existing hyperplasia.

Nucleic acid-mediated therapy and in vivo vector targeting

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

Because the instant claims do not limit the site of delivery of nucleic acids, relative to the site to be treated, the claims embrace systemic intravascular delivery of the therapeutic nucleic acid compositions. However, while progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired sites continues to be unpredictable and inefficient.

This is supported by numerous teachings available in the art. For example, Miller (1995) reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998) reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma (1997) clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Verma discusses the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239 and 2nd and 3rd column of page 242. Verma also indicates that appropriate enhancer-promoter sequences can improve expression, but that the "search for such [useful] combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). Crystal (1995) also reviews various vectors known in the art and indicates that "among the design

hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). While the specification supports efficient transfer for direct application of nucleic acids to the site of intimal thickening in a rabbit, the specification fails to teach one of skill in the art how to overcome the unpredictability for vector targeting such that efficient gene transfer is achieved by any other mode of delivery. The specification fails to teach any specific targeting techniques, fails to provide any working examples which encompass vector targeting, and fails to direct the skilled artisan to any teachings of targeting strategies known in the art which would allow one of skill in the art to practice the claimed invention without undue experimentation.

With specific respect to therapies based on the transfer of VEGF to the arterial wall, Laitinen (Pharm. Res. 47(4): 251-254, 4/1998) teaches that although promising effects on cardiovascular diseases have been noted by adventitial delivery of genes in animal models using the collar device disclosed at page 16, lines 21-23 of the specification, "further studies regarding gene transfer techniques, vectors, and safety of procedures are needed before a full therapeutic potential of gene therapy in vascular diseases can be evaluated." See abstract. See also sentence bridging pages 252 and 253, and last sentence of CONCLUSIONS on page 253. Thus the treatment of vascular diseases in general by delivery of VEGF nucleic acids was unpredictable at the time the invention was filed.

Relevance of animal models of intimal hyperplasia to human disease and treatment

The prior art teaches that successful treatment of intimal hyperplasia in small animal models is not predictive of success in other animals, particularly in humans. Muller et al (J. Amer. Coll. Cardiol. 19(2):418-432, 1992) teach that, as of 1992, greater than 50 studies had shown that at least 9 different classes of pharmacological agents inhibit intimal proliferation in response to arterial injury in animal models. However, none of these agents reproducibly reduced the incidence of restenosis after coronary balloon angioplasty in humans. To explain these results, Muller considered the differences between the various systems. Significant interspecies and intraspecies differences were found to exist among the various animal models, particularly with respect to the extent and composition of neointimal thickening, drug and lipid metabolism, and the activity of coagulation and fibrinolytic systems. The instant specification teaches a single example of inhibition of intimal thickening at the precise site of VEGF expression vector administration in a rabbit model of intimal hyperplasia. See Example 1, pages 33-38. The specification teaches no example of complete prevention or reversal of intimal hyperplasia in any model. With respect to rabbit models, Muller notes that rabbit arteries are not necessarily structurally equivalent to human arteries. For example, the amount of elastin in the media of coronary arteries is less than that in larger mammals, the intima is thinner, and the subendothelial space between the endothelium and the internal elastic lamina is very narrow and virtually acellular. A similar intimal structure is found in the arteries of humans only during fetal and early neonatal life. See paragraph bridging columns 1 and 2 on page 420. Muller teaches that these differences may account for the variability in sensitivity of various animal models to treatments, and should be

considered carefully in the interpretation of experimental studies. See abstract. Also, after reviewing rat, rabbit, dog, non-human primate, and pig models Muller found that it was "clear that there are major differences among the animal models, particularly in terms of the nature of arterial injury and the composition of the neointima. It could be expected, therefore, that a pharmacological therapy that is effective in one animal model may be ineffective in another species or in humans." See page 426, column 2, first full paragraph. Thus Muller clearly indicates that results in one animal model are not necessarily predictive of results in another animal model due to physiological differences between the models.

Lafont et al (Ann. Card. Ang. 44(7): 349-353, 9/1995), reviewed the results of fifteen years of research prior to 1995, and conclude that "[a]ll the restenosis strategies based on inhibition of smooth muscle cell proliferation, which successfully limited restenosis in animal models have failed in man, due to hazardous extrapolations from experimental models which are very different from the atheromatous lesions observed in man". See abstract. Lafont et al (Card. Res. 39(1): 50-59, 7/1998) further indicates that while animal models may be useful for determining the mechanism of a drug on smooth muscle cell proliferation, positive results should not be interpreted to mean that a given treatment will function in humans. "The extrapolation of animal studies directly to man is unreasonable given the vast differences between animal models and man, and the complexity of the restenotic process." See page 54, column 2, lines 3-12. In fact, the unpredictability in extrapolating results of such studies to humans was noted as late as 1999, when Johnson et al taught that small animal models "lacked efficacy in predicting the

success of interventions to inhibit restenosis in humans", and found that small animal models fail to closely simulate human atherosclerosis and stenotic lesions. See abstract. For these reasons, even if the specification provided adequate guidance to one of skill in the art to practice the full scope of the invention in rabbits, which it does not, the enabled use of the claimed invention would be limited to the treatment of rabbits.

Action of Flt-1 and Flk-1/KDR receptor agonists

The specification teaches that the invention may be practiced with any Flt-1 and Flk-1/KDR receptor agonist. Disclosed receptor agonists include HIV TAT (pages 11 and 12) various splicing alternatives of VEGF, and placental growth factor (PIGF). The prior art teaches that PIGF is a Flt-1 receptor agonist. See e.g. Park et al (J. Biol. Chem. (1994 Oct 14) 269 (41) 25646-54) abstract. However, the specification at page 45, lines 6 and 7 discloses that PIGF elicits different cellular responses than VEGF, even though it binds the same receptor. Furthermore, Khaliq et al (Laboratory Investigation 79(2): 151-170 (1999)) showed that PIGF-1 and PIGF-2 exert different effects through the same Flt-1 receptor. Importantly, Khaliq showed that PIGF-2 inhibits the basal release of NO. The specification teaches at page 5, lines 24-28 that the invention functions at least in part by the NO pathway, and that VEGF stimulates NO production. So, one of skill in the art would not expect PIGF-2 to function in the invention because, even though it is a Flt-1 receptor agonist, it has the opposite effect of VEGF on NO production. Given the preceding discussion, one of skill in the art would conclude that the effects of a given receptor ligand can vary with the identity of the ligand, and that not all ligands

will have identical activities in terms of signal transduction. It is apparent that not all Flt-1 and Flk-1/KDR agonists will function in the invention, and the specification has failed to provide any theoretical framework as to how to establish which agonists will function as intended. One might argue that it would not be undue experimentation to assay agonists individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Because Applicant has provided no basis for predicting which agonists will function as intended in the invention, and because one of skill in the art would recognize this to be unpredictable based on the state of the art of VEGF receptor agonists, the specification does not adequately enable the full breadth of the claims.

In summary, at the time of the invention, those of skill in the art recognized that one could not accurately extrapolate positive results from small animal models of smooth muscle cell proliferation to other animals, particularly humans; the specification fails to provide guidance that would allow such extrapolation; the specification exemplifies only inhibition of hyperplasia in a rabbit model, and not complete prevention or reversal of hyperplasia; the specification fails to provide any working example of treatment in any organism other than a rabbit; the specification fails to teach how to perform the claimed methods by delivering nucleic acids to any site other

than a site of intimal thickening; and the specification fails to adequately teach which Flt-1 and Flk-1/KDR receptor agonists will function as intended. For these reasons, one of skill in the art could not practice the claimed methods commensurate in scope with the claims without undue experimentation.

Response to Arguments

Applicant's arguments filed 3/5/03 have been fully considered but they are not persuasive. Applicant asserts at page 2 of the response that the Declaration of Dr. Martin, filed 11/25/02 shows that a nucleic acid encoding VEGF was successfully delivered to and expressed in pig blood vessel cells. Applicant argues that an application is not required to show that clinical efficacy is achieved, and that the Declaration is evidence of enablement.

This is unpersuasive for several reasons. First, although Applicant is not required to show that clinical efficacy is achieved, Applicant must teach how to use the invention commensurate in scope with the claims. In view of the state of the art of treating intimal hyperplasia, the unpredictability of this art, the fact that those of skill in the art find the animal models to be unsatisfactory, and the failure of the specification to provide adequate guidance to overcome these barriers to success, one of skill in the art would have to perform undue experimentation in order to practice the claimed invention commensurate in scope with the claims.

Second, although the specification teaches a working example in rabbits, the results of the experiment summarized in the Declaration suggest that the invention is inoperable in pigs. The

Declaration presents the results of an experiment in which nucleic acids encoding VEGF-D were delivered **at the site of surgery** in pigs which had undergone surgical anastomosis of the carotid artery and internal jugular vein. As discussed in the specification at page 1, lines 18-23, surgical treatments like this and angioplasty can give rise to intimal hyperplasia at the site of surgery or balloon-induced damage. For this reason, any significant results of the experiment could support only methods in which the nucleic acid was delivered **to the site of damage**. In contrast, the claims as amended require only that the nucleic acid must be delivered to the blood vessel, and fail to require delivery to the site of intimal hyperplasia in that blood vessel. As applicant clearly understands, the carotid artery on which the experiments were performed is several inches long. There is no reason to expect that nucleic acids delivered to cells several inches from the site of injury on the same vessel will have any effect on the cells in the injured area, yet the claims continue to embrace that as an embodiment of the invention. The specification suggests that therapeutic effect of the method owes to production of NO or prostacyclins. However, the specification fails to teach how much of any VEGFR agonist is required to produce sufficient NO or prostacyclin for any effect, how to produce the appropriate amount of the agonist *in vivo,* or how to deliver appropriate amounts of NO or prostacyclin from transfected cells to target cells that are not located **at the site** of transfection. Furthermore, the Declaration provides no statistical analysis of the results, the sample size is small, and the results indicate that the treatment may in fact increase intimal hyperplasia over time. See in particular, page 5, first sentence of paragraph 4 which indicates that at day 60 there was an increased degree of intimal

proliferation/fibrosis and a reduction in luminal diameter in the groups which received VEGF-D adenovirus, when compared with the controls, and that luminal occlusion occurred only in animals treated with VEGF-D. Finally, because intimal hyperplasia is known to occur in about 30% of arterial bypasses after two years (see specification at page 2, lines 10 and 11), it is not clear that an inhibition of intimal proliferation in 50% of individuals at 28 days after surgery is significant at all, particularly in view of the small sample size and the fact that after 60 days intimal proliferation and luminal occlusion increased in VEGF-treated individuals. In other words, if one would expect 70% of individuals to be unaffected by restenosis normally, it does not seem significant that intimal proliferation was inhibited in 50% of pigs. If the described pig model generally results in a higher frequency of restenosis such that inhibition of intimal proliferation in 50% of individuals could be considered significant, then Applicant should make this clear.

At page 3, Applicant argues that the rabbit is an art-accepted animal model, relying for support on Strauss (202) and Farb (2001), and asserting that if the rabbit model was not a suitable model clinical researches would not use it in their studies. This is unpersuasive because the Office has established that, at the time the invention was filed, no drug treatment developed in a small animal model had ever been used to successfully treat intimal hyperplasia in humans. As discussed in the rejection, this is because intimal hyperplasia in humans is a physiologically different process taking place in physiologically different structures than in the animal models such as the rabbit. The fact that animal models are used for research does not mean that the results obtained in these animal models will be applicable to humans, and the evidence of record shows

that the results in animal models of hyperplasia both before and after the time of the invention were not applicable to humans. Applicant has presented no reasoning as to why the findings of Muller (1992), Lafont (1995), Lafont (1998), and Johnson (1999) regarding the physiological differences between various animals and the lack of suitability of small animal models of intimal hyperplasia and restenosis should be cast aside. For these reasons the rejection is maintained.

Written Description

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-9 embrace the genus of agonists of Flt-1 and Flk-1/KDR receptors that can inhibit restenosis. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species has been described by complete structure, such as nucleotide sequence, next it is determined whether a representative number of species has been described by other relevant identifying characteristic. In this case, the specification discloses VEGF and its splicing alternatives, HIV TAT, and PIGF. However, as noted above under enablement, the function of Flt-1 and Flk-1/KDR receptor agonists within the context of the invention is highly unpredictable. For example, the specification at page 45, lines 6 and 7 discloses that PIGF elicits different cellular responses than VEGF, and Khaliq et al

(Laboratory Investigation 79(2): 151-170 (1999)) showed that PIGF-1 and PIGF-2 exert different effects through the same Flt-1 receptor. Importantly, Khaliq showed that PIGF-2 inhibits the basal release of NO. The specification teaches at page 5, lines 24-28 that the invention functions at least in part by the NO pathway, and that VEGF stimulates NO production. So, one of skill in the art would not expect PIGF-2 to function in the invention because, even though it is a Flt-1 receptor agonist, it has the opposite effect of VEGF on NO production. Given the preceding discussion, one of skill in the art would conclude that the effects of a given receptor ligand can vary with the identity of the ligand, and that not all ligands will have identical activities in terms of signal transduction. It is apparent that not all Flt-1 and Flk-1/KDR agonists will function in the invention, and the specification has failed to provide any theoretical framework as to how to establish which agonists will function as intended. It is unclear from the specification, and unpredictable in view of the prior art, whether or not HIV TAT would function to inhibit intimal hyperplasia. Therefore the specification has disclosed a single species of receptor agonist (VEGF) which would predictably function as intended. (The splicing alternatives of VEGF are considered to be sub-species). The specification fails to disclose any relevant identifying characteristic, such as a any correlation between structure and function, that would convey to one of skill in the art that Applicant was in possession of the genus of Flt-1 and Flk-1/KDR receptors that can inhibit restenosis. Furthermore the on the Guidelines on Written Description (published December 21, 1999 in the Federal Register, Volume 64 Number 244, pp. 71427-71440 (also available at

www.uspto.gov)) provide clear guidance in situations where only a single species is disclosed in an unpredictable art.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.
>
> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. **In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.**

Because the specification discloses only a single species of VEGF receptor which would predictably function as intended, and because the art in question would be recognized by those of skill in the art as unpredictable, one of skill in the art could not conclude that Applicant was in possession of the claimed invention at the time of filing.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-6 and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Laitinen et al (Circulation (10/15/96) 94(8): 3720).

Laitinen teaches inhibition of intimal proliferation in a rabbit artery in vivo by periadventitial delivery of a nucleic acid encoding VEGF. The artery was not denuded of its epithelium. See abstract.

Thus Laitinen anticipates the claims.

It is noted that while each of the instant inventors is an author of this document, others are also cited as authors, i.e. Pakkanen, Luoma, Laakso, Breier, Risau, and Soma. Therefore the inventive entity differs from the authorship, so the invention was known to "others" within the meaning of 35 USC 102(a). See MPEP 2132 (III).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asahara et al (Circulation (1996) 94(12): 3291-3302), in view of Mayberg (US Patent 6,326,017, issued

12/4/2001), Goldstein et al (US Patent 5,962,427 issued 10/5/99) and Gilbert et al (Archives of Otolaryngology (1989) 115(8): 970-976).

Asahara teaches that intimal hyperplasia in rabbits can be inhibited by delivering to an injured artery a plasmid encoding human VEGF 165 (instant SEQ ID NO: 4). See abstract.

Asahara does not teach periadventitial delivery to an artery with an intact epithelium.

Mayberg teaches methods for localized delivery of agents to arteries. The methods comprise applying to the external surface of an artery a polymer matrix comprising the agent, and then covering the polymer matrix with a barrier adapted to restrict the release of the agent into the artery. See claims 1-4, and column 3, lines 22-26. The method provides high concentrations of the agent at the site of action. See column 2, lines 23-32. Mayberg teaches that the polymer may be a PLGA polymer. See column 4, lines 18-30, especially lines 25 and 26. Because the polymer matrix is applied to the external surface of the artery, administration is considered to be periadventitial.

Goldstein teaches PLGA compositions for the controlled release of nucleic acids into cells in vivo. See e.g. claim 1 at column 36 and column 12, lines 31-36.

Gilbert teaches a rabbit model of intimal hyperplasia induced by surgical anastomosis. See abstract. Because the model does not involve denudation or destruction of the endothelium, the endothelium is presumed to be intact. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to apply to the adventitial surface of a hyperplastic artery of Gilbert a PLGA polymer as taught by

Mayberg, wherein the polymer comprised the nucleic acid of Asahara. One would have been motivated to do so in order to inhibit intimal hyperplasia in the rabbit model. One would have been motivated to use the invention of Mayberg to deliver the nucleic acid of Asahara because Mayberg teaches that it provides a high local concentration of an agent one wishes to be delivered. One could have done so with a reasonable expectation of success because PLGA polymers are routinely used to delivery DNA in vivo, as evidenced by Goldstein.

Thus the invention as a whole was *prima facie* obvious.

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Asahara et al (Circulation (1996) 94(12): 3291-3302), in view of Mayberg (US Patent 6326017, issued 12/4/2001) and Gilbert et al (Archives of Otolaryngology (1989) 115(8): 970-976) as applied to claims 1-8 above and further in view of Janjic et al (US Patent 5,859,228, issued 1/12/1999).

The teachings of Asahara (1996), Mayberg (2001), and Gilbert (1989) are summarized above, and render obvious methods of inhibiting in a rabbit intimal hyperplasia by delivering periadventitially to arteries with intact epithelium nucleic acids encoding human VEGF 165 (SEQ ID NO: 4).

These references do not teach the isoforms of VEGF corresponding to SEQ ID NOS< 2, 6, and 8.

It would have been similarly obvious to substitute for the human VEGF 165 nucleic acid other nucleic acids encoding human VEGF 121 (SEQ ID NO:2), VEGF 189 (SEQ ID NO:6), or

VEGF 206 (SEQ ID NO:8) because Janjic teaches that these isoforms of VEGF all bind the same receptors. See column 6, lines 8-25. Thus, one would reasonably expect these isoforms to have similar effects in the invention. As such they are considered to be obvious variants of each other. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 7, and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laitinen et al (Circulation (1996) 94(8): 3720), in view of Janjic et al (US Patent 5,859,228, issued 1/12/1999).

Laitinen teaches inhibition of intimal proliferation in a rabbit artery in vivo by periadventitial delivery of a nucleic acid encoding VEGF. The artery was not denuded of its epithelium. See abstract.

Laitinen is silent as to the source of the VEGF used in the procedure and so is not relied upon to teach nucleic acids encoding human VEGF, or VEGFs 121, 165, 189, or 206 (SEQ ID NOS: 2, 4, 6, or 8).

It would have been obvious to use any of nucleic acids encoding human VEGF 121 (SEQ ID NO:2), VEGF 165 (SEQ ID NO: 4), VEGF 189 (SEQ ID NO:6), or VEGF 206 (SEQ ID NO:8) because Janjic teaches that these isoforms of VEGF all bind Flk-1/KDR receptors as required by the instant claims. See column 6, lines 8-25. Thus, one would reasonably expect these isoforms to have similar effects in the invention. As such they are considered to be obvious variants of each other and of the VEGF used by Laitinen. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit

1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.